Receptive field dynamics in adult primary visual cortex

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THE adult brain has a remarkable ability to adjust to changes in sensory input. Removal of afferent input to the somatosensory, auditory, motor or visual cortex results in a marked change of cortical topography[1–10]. Changes in sensory activity can, over a period of months, alter receptive field size and cortical topography[11]. Here we remove visual input by focal binocular retinal lesions and record from the same cortical sites before and within minutes after making the lesion and find immediate striking increases in receptive field size for cortical cells with receptive fields near the edge of the retinal scotoma. After a few months even the cortical areas that were initially silenced by the lesion recover visual activity, representing retinotopic loci surrounding the lesion. At the level of the lateral geniculate nucleus, which provides the visual input to the striate cortex, a large silent region remains. Furthermore, anatomical studies show that the spread of geniculocortical afferents is insufficient to account for the cortical recovery. The results indicate that the topographic reorganization within the cortex was largely due to synaptic changes intrinsic to the cortex, perhaps through the plexus of long-range horizontal connections.

By comparing receptive field size and position for identical cortical sites in the primary visual cortex monitored before, immediately after (Fig. 1) and months after (Figs 2 and 3) making the retinal lesions, we were able to determine the nature of the changes occurring in the short and long term. Dramatic changes were observed even minutes after the lesion: those sites with receptive fields located close to the centre of the lesion were made unresponsive, but at recording sites where the fields were originally close to and just inside the lesion boundary, there was a large increase in receptive field area. In the experiment illustrated in Fig. 1, receptive field maps of cells in the superficial cortical layers recorded before making the lesion expanded fivefold in area. The expanded fields were well outside the normal range of field sizes of superficial layer cells at this eccentricity. Though the change in field size was the most obvious effect, there was also a small centrifugal shift in field positions from the centre of the lesion. The shift might simply reflect field enlargement combined with a removal of one side of the field by the lesion, resulting in an apparent shift. Though slight shifts of field position do tend to occur as a result of eye movement, in this and other experiments we revisited a subset of the sites (about 1/5 of the total) before lesioning to establish the repeatability of the measurements of size and position, and demonstrated their stability within the recording session relative to the changes observed following the lesion. Furthermore, the consistent centrifugal shifts in position argue against attributing them to random eye movements. Results analogous to our observations in visual cortex were reported in the flying fox somatosensory cortex following digit amputation[12], and in motor cortex following sensor-motor nerve transection[4,13], with immediate changes in cortical topography and, in somatosensory cortex, increase in receptive field size as well. In our experiments the properties of the expanded receptive fields were similar to

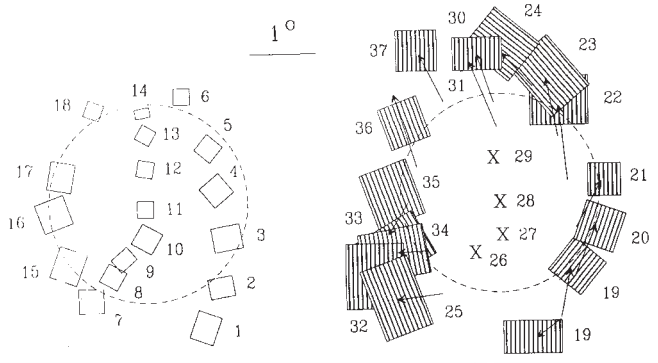

FIG. 1 Receptive fields of cells encountered in vertical electrode penetrations in the superficial layers of monkey area V1 before and immediately after binocular retinal lesions at retinotopically corresponding sites. The first sets of receptive field maps, made before the lesion, are shown on the top left, with the subsequently made lesion included for reference (dashed lines). The size and retinotopic positions of the receptive fields encountered in one animal within minutes after making the lesion are shown at the top right. Using the cortical vasculature for reference (bottom), the same recording sites were visited before and after the lesion so one could make a direct comparison of the receptive fields of cells enocuntered at these sites at the different time points. The recording sites made before the lesion (small dots) and after the lesion (large dots) are numbered, with the corresponding receptive fields numbered accordingly. On the same day of the lesion a number of the originally recorded cortical sites were unresponsive to visual stimuli (as indicated by the *X*s on the right figure). The most striking effect was that receptive fields originally located near the boundary of the lesion have greatly expanded, on average reaching 5 times their original area: before the lesion, the average field area at the recording sites was 0.07 deg^2 (±0.03 deg^2), and 0.37 deg^2 (±0.26 deg^2) immediately after the lesion was made ($p \ll 0.01$). In addition, there was a suggestion of a shift in receptive field position from immediately inside, to just outside the boundary of the lesion, although this shift was less than 1°. The arrows in the top right indicate the relative positions of the receptive field centres of cells at nearby cortical sites recorded before and after the lesion, with the starting centre position of each receptive field indicated by the tail end of the arrow, and the ending position by the arrow head. A few of the arrow positions were interpolated at points where the before and after recording sites were not sufficiently close. The position of the fovea is indicated by the Xs at the top of the figure.

METHODS. Electrophysiology and lesioning procedures were done in anaesthetized, paralysed cats and monkeys (anaesthetic, sodium pentothal; paralytics, Norcuron for monkeys, succinylcholine for cats; anaesthesia level monitored by electroencephalography). A total of 12 pairs of lesions were made at corresponding sites in the two retinae of 6 monkeys and 8 pairs of lesions in 4 cats. Receptive field maps, made with hand-held stimulator, are 'minimum response' fields for cells in the superficial layers, obtained with a light bar generated by a hand-held projector, and were mapped independently for each eye. In each experiment, a selected region of cortex was mapped, within this region a site was chosen so that the receptive fields would be centred within the lesion, which was made in the parafoveal retina with a diode laser directed through an indirect opthalmoscope (Iris Instruments; 400 mW × 500 μs). Lesions of this strength and duration destroyed primarily the outer retina, leaving the retinal ganglion cell layer intact, as later determined by post mortem histology in each animal. In monkeys, the lesions were centred 3 to 5° below the fovea near the midline, and were 1 mm, or 3 to 5° in diameter. In cortical terms, this produced a region of unresponsive cells ~8 mm in diameter. The visuotopic boundaries of the lesions were mapped by back projecting the beam from a Nikon fundus camera to the tangent screen on which the receptive fields were mapped, enabling us to determine the positions of the receptive fields relative to the lesion. Using the cortical vasculature for reference, another series of electrode penetrations was made at the original mapping sites immediately following the lesion.

those seen in normal cortex, including orientation selectivity, directionality and binocularity.

To compare the long term effects of laser lesions with those observed on the same day as the lesion, we followed the course of receptive field structure and cortical topography for two months following the lesion. At the end of this period, all cortical sites could be activated by visual stimuli, but in comparison with the map made before the lesion, we observed large shifts in field position, up to 5°, for those recording sites with fields originally located at the centre of the lesion (Fig. 2). As described previously, this resulted in a great expansion of the representation of the perilesion retina[8-10]. In several experiments we observed shifts in field position for cells situated at cortical sites originally representing parts of the retina outside the lesion. Other receptive field anomalies were also observed, including bipartite receptive fields spanning the lesion, fields in the ipsilateral visual field (presumably generated by callosal input), and shifts in different directions for the two eyes. These effects and the accumulation of fields at the edge of the lesion would not be seen in the cortices of unlesioned animals. For the experiment illustrated in Fig. 2, the receptive fields in the recovered cortex were severalfold larger than normal. The ratio of expansion was not as great as that seen immediately after the lesion, suggesting that the initial expansion is followed by a consolidation in the long term.

The alterations of cortical topography in adult animals first seen in the somatosensory cortex following digit amputation have now been demonstrated in studies of various sensory and motor areas[1-10]. A persistent question is whether the locus of change is at the cortical level or at a prior stage in the sensory pathway. Earlier studies have shown topographical shifts at the subcortical level resulting from deafferentation[14]. By the same token, retinal lesions can change the topography of the lateral geniculate nucleus (LGN), though the changes shown previously were small (limited to 200 μm)[15]. By comparing the topographical changes in the LGN and cortex in the same animal, at the same time and with the same type of lesion, we were able to determine that most of the long-term cortical changes seen in the current study originated in the cortex: in two cats (the results from one are illustrated in Figs 3 and 4) and one monkey, at a time when the initial cortical scotoma had disappeared (Fig. 3), there was still a large unresponsive area in the LGN (about 1 mm in diameter, corresponding topographically to the size of the retinal scotoma). The expected extent of the affected area in the LGN was determined by making two injections of different retrograde tracers in the cortex on either side of the original cortical scotoma. Electrode penetrations between the clusters of labelled cells in the LGN showed no visually activated cells (Fig. 4*c*). None of the other features of the cortical reorganization, such as an enlarged representation of perilesion retina, enlarged or bipartite fields, was observed in the LGN (Fig. 4*a*). Finally, the lack of overlap in the distributions of the two clusters of labelled cells suggested that the fill in of the cortical scotoma was not mediated either by the normal spread of geniculate afferents within the cortex, or by their sprouting into the cortical scotoma.

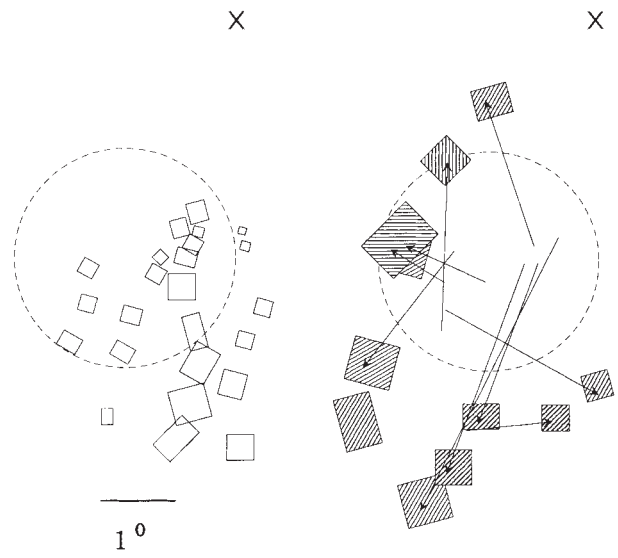

FIG. 2 Receptive field maps in a region of monkey cortex deafferented by a retinal lesion, immediately before the lesion was made (left) and two months following the lesion (middle). This was done in a different animal from the one illustrated in Fig. 1. A much larger shift in receptive field position is seen at two months than in the immediate-term experiments, with the cortical scotoma having entirely filled in. All recorded sites had cells with receptive fields located outside the lesioned retinal area, although a few fields did overlap with the scotoma, probably owing to incomplete destruction at the edge of the scotoma in the retina. Although some arrows are crossed, overall the shifts maintained a rough retinotopic order, with fields that were originally located in the lower part of the scotoma shifting down, and those located in the upper part shifting up. Note that for one site where the receptive field was initially located outside the lesion, the field shifted horizontally. This result was observed in several experiments, and indicates that the effects of the perturbation caused by the lesion are propagated beyond the deafferented area of cortex. There was also receptive field enlargement, though less than that observed in the short-term experiment shown in Fig. 1: the field areas averaged 0.036 deg^2 (±0.022 deg^2) before the lesion and 0.100 deg^2 (±0.025 deg^2) two months later ($P \ll 0.01$). The Xs mark the foveal position.

The transmission of visual information from one visual field locus to another, taking place at both the immediate and long term in the cortex, may instead be mediated by the long-range horizontal connections[16-20]. These connections have been implicated in dynamic, contextually dependent changes in the

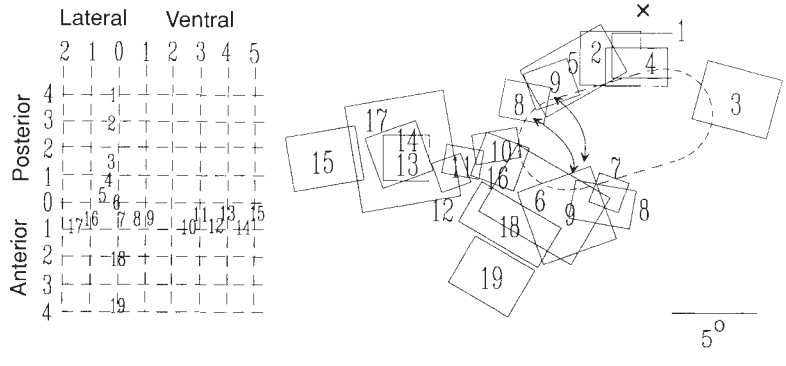

FIG. 3 Mapping of cat visual cortex 2 months after binocular retinal lesions. At this time the cortical scotoma has entirely filled in. The right of the figure shows the receptive field maps and lesion boundary, and the left part shows the Horseley–Clarke coordinates of the recording sites (mm), which are numbered. The initial cortical scotoma was centred at site 7. With regular shifts in recording position from posterior to anterior (sites 1 to 7, 18 and 19) and from lateral to medial (sites 17 to 7, lying in area 18, and sites 7 to 15 corresponding to a tangential electrode penetration down the medial bank of the lateral gyrus, within area 17) all sites were activated by visual stimuli. Nearby sites (5 and 6) had fields lying on opposite sides of the lesion, and the receptive field positions tended to accumulate around the perilesion retina. Other field anomalies were observed, including bipartite fields, with subfields lying on either side of the scotoma (8 and 9), fields lying in the ipsilateral visual field (3), and fields in different positions in the two eyes (not shown). The receptive field maps and lesion boundary (dashed line) are shown for one eye only. X marks the centre of the area centralis.

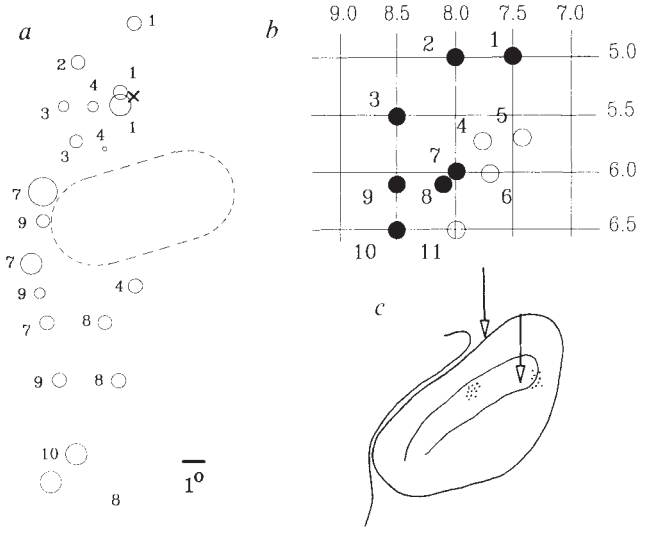

FIG. 4 Mapping of cat lateral geniculate nucleus in the same animal showing fill-in of the cortical scotoma illustrated in Fig. 3. At the two-month time point, a 1-mm wide silent area remained in the LGN. *a*, Receptive field maps of cells encountered in multiple penetrations shown in *b*. In penetration 4, there was a regular shift in receptive field position up to the edge of the scotoma, followed by a 1-mm-long zone of silence, followed by a resumption of activity on the other side of the scotoma. None of the characteristics seen in the recovered cortex, such as an overrepresentation of the perilesion retina, enlarged fields at the edge of the scotoma or bipartite fields, was seen in the LGN. *b*, Positions of penetrations in the LGN in Horseley–Clarke coordinates (mm). Several of the penetrations, covering an area ~1 mm wide, encountered visually unresponsive cells within the geniculate (open circles). Surrounding this area the electrodes encountered visually responsive cells (closed circles). *c*, Coronal view of a section through the LGN. Injections of red and green fluorescent latex microspheres (Lumafluor) were made on either side of the original cortical scotoma after the two-month survival to label the expected boundaries of the scotoma in the LGN (clusters of dots). The mapping and histology were done two weeks after the injections. Penetrations between the clusters at this antero-posterior level (open arrows) encountered visually unresponsive cells, demonstrating a sizable retained geniculate scotoma at a time when all parts of the cortex could be activated by visual stimuli. The lack of overlap between the clusters suggests further that the filling in seen in cortex is not likely to be mediated by the spread of geniculate afferents within the cortex.

response properties of cortical cells[21]. Our results suggest that the subthreshold influences of horizontal connections can be potentiated to be capable of activating the cell. The magnitude of the topographical shifts, roughly 4 to 5 mm, are large relative to the lateral spread of thalamic afferents, but the horizontal connections have an extent sufficient to account for such a reorganization. Furthermore, they are specific in connection columns of similar orientation specificity[22–24], and could explain the orientation selectivity observed in the reorganized cortex. The receptive fields seen in the ipsilateral visual field are likely to come from the contralateral hemisphere by way of the corpus callosum.

Perhaps even more surprising than the reorganization seen in the long term are the short-term changes in receptive field size and topography. Stimulus-dependent changes in receptive field size have been observed in the somatosensory cortex, where repeated stroking of a body part over a period of months leads to a decrease of receptive field size[11], in effect the opposite of the type of experiment done here. Our results suggest that the subthreshold influences from outside the classical receptive field can be quickly unmasked when the ascending input is inactivated, and these short term effects represent a surprising degree of plasticity of cortical topography and receptive field structure for adult animals. The immediate changes may represent the neural substrate of perceptual phenomena such as surface fill-in of colour and texture[25–29], illusory contours[30], and learning effects[31,32], and raises the possibility that dynamic changes in receptive field structure may occur continuously during normal vision. □

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Genetic immunization is a simple method for eliciting an immune response

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TO produce an immune reaction against a foreign protein usually requires purification of that protein, which is then injected into an animal. The isolation of enough pure protein is time-consuming and sometimes difficult. Here we report that such a response can also be elicited by introducing the gene encoding a protein directly into the skin of mice. This is achieved using a hand-held form of the biolistic system[1–4] which can propel DNA-coated gold microprojectiles directly into cells in the living animal[3,5,6]. Genetic immunization may be time- and labour-saving in producing antibodies and may offer a unique method for vaccination.

Young (8–15 weeks old) mice were inoculated in the ear with microprojectiles coated with plasmids containing the genomic copy of the human growth hormone (hGH) gene under the transcriptional control of either the human β-actin promoter[7] or the cytomegalovirus (CMV) promoter[8]. Production of antibody directed against hGH was monitored by assaying sera from tail-bleeds for the capacity to immunoprecipitate ^{125}I-labelled hGH. Figure 1 depicts the time-course of appearance

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